A cross-sectional study contrasting olfactory function in autonomic disorders

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ABSTRACT

Objective: To compare odor identification function in patients with peripheral or central autonomic neurodegeneration and in patients with intact autonomic neurons but undetectable norepinephrine.

Methods: Olfactory function was evaluated with the University of Pennsylvania Smell Identification Test (UPSIT) in 12 patients with pure autonomic failure, 10 patients with multiple system atrophy, and 4 patients with dopamine β-hydroxylase deficiency. Blood pressure and catecholamine data were also compared.

Results: Odor identification was significantly impaired in patients with pure autonomic failure relative to patients with multiple system atrophy or dopamine β-hydroxylase deficiency. Out of 40 odors, the patients correctly identified mean (95% confidence interval) 19.2 (14.1 to 24.2), 34.4 (32.2 to 36.6), and 31.7 (29.4 to 34.1) ($p < 0.001$). The difference between patients with pure autonomic failure and those with multiple system atrophy or dopamine β-hydroxylase deficiency persisted after adjustment for age ($p = 0.001$). Patients with pure autonomic failure also had a greater orthostatic fall in blood pressure and lower plasma norepinephrine levels than patients with multiple system atrophy.

Conclusions: Olfactory function was relatively intact in patients with dopamine β-hydroxylase deficiency, who have intact noradrenergic neurons but lack norepinephrine. Odor identification was impaired in pure autonomic failure but not in multiple system atrophy, suggesting that 1) peripheral noradrenergic innervation is important for olfactory identification but norepinephrine is not essential and 2) UPSIT may be useful in the differential diagnosis between these disorders.
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GLOSSARY

CI = confidence interval; **DBHD** = dopamine β-hydroxylase deficiency; **DHPG** = dihydroxyphenylglycol; **MSA** = multiple system atrophy; **PAF** = pure autonomic failure; **PD** = Parkinson disease; **UPSIT** = University of Pennsylvania Smell Identification Test.

Although pure autonomic failure (PAF) and multiple system atrophy (MSA) are both rare autonomic disorders, MSA is more progressive and more rapidly fatal than PAF. A test able to distinguish PAF from MSA would therefore be useful. While cardiac neuroimaging studies may be an effective means to determine whether a patient has PAF or MSA,[1,2] this procedure is not readily available.[3]

The University of Pennsylvania Smell Identification Test (UPSIT) has been used in the preclinical diagnosis of Parkinson disease (PD).[4,5] Pathophysiologically, PD and PAF are part of the same disease spectrum,[6,7] and UPSIT scores are similarly reduced in patients with PAF and PD.[1] Correlation studies suggest that the UPSIT could be used as an alternative to neuroimaging in the differential diagnosis of MSA vs PD or PAF, although data on olfactory function in MSA are conflicting.[8-10]

The study of patients with autonomic disorders can improve our understanding of olfactory function. The primary lesion in PAF is in the peripheral autonomic nervous system, whereas MSA is

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a central neurodegenerative disease, so impaired smell in PAF but not in MSA would suggest that peripheral noradrenergic innervation is important for olfactory identification. Patients with dopamine β-hydroxylase deficiency (DBHD) have intact central and peripheral noradrenergic neurons, but their neurons release dopamine instead of norepinephrine.[11,12] DBHD can thus provide insight about the neurotransmitters involved in odor identification.

This study assessed 1) whether olfactory function, as measured by the UPSIT, differs between patients with PAF and MSA and 2) whether olfactory identification is affected by the lack of norepinephrine in patients with DBHD.

METHODS

Standard protocol approvals and patient consents. A total of 12 patients with PAF, 10 patients with MSA, and 4 patients with DBHD were studied. Each gave written informed consent prior to testing, and the protocol was approved by the Vanderbilt Institutional Review Board. One additional patient with MSA and one additional patient with PAF failed to complete the test protocol.

Study populations. We conducted a cross-sectional study in which participants were recruited for UPSIT testing from patients evaluated in the Vanderbilt Autonomic Dysfunction Center between 2004 and 2010. Following an overnight supine rest and while fasted, supine and standing oscillometric brachial blood pressures were measured and venous blood samples were collected for fractionated catecholamines.[13]

Patients with PAF demonstrated impaired sympathetic and parasympathetic function in standardized autonomic function tests,[14] recurring orthostatic hypotension, and reduced catecholamine levels, without cerebellar, striatal, pyramidal, or extrapyramidal dysfunction. Patients with MSA met the criteria for probable MSA.[15] Patients with DBHD described lifelong orthostatic and exercise intolerance and demonstrated the characteristic catecholamine pattern, with undetectable norepinephrine and epinephrine and greatly elevated dopamine.[16]

Odor identification testing. The American-English version of the UPSIT (Sensonics, Inc., Haddon Heights, NJ) was applied during inpatient evaluations in 8 participants (3 PAF, 2 MSA, and 3 DBHD) and mailed to the homes of the remaining subjects. In addition to the absolute score (number of odors identified correctly out of 40), an individual was assigned to a category (normosmia; mild, moderate, or severe microsmia; anosmia; or probable malingering) based on previously established norms for gender and age.[17] Inpatients were off medications while those who took the test at home remained on their usual medications. Information regarding smoking history and medication usage was obtained as part of the UPSIT test.

Statistical analyses. Data are expressed as mean (95% confidence interval [CI]). Differences between patient groups were assessed by the Kruskal-Wallis test (3 groups) or by the Mann-Whitney *U* test (2 groups). To determine if the smell score was associated with age in PAF and MSA, a regression analysis was run with the UPSIT score as outcome variable and age and diagnosis as covariates. The χ^2 test was used for analysis of categorical variables. Statistical analyses were carried out using the statistical software SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL). All tests were 2-sided and differences with $p < 0.05$ were considered significant.

RESULTS

Subject characteristics. All patients were white, with the exception of one patient with PAF, who was Hispanic. Patient groups were evenly mixed by gender. Patients were diagnosed at a mean (95% CI) age of 62.7 (56.5 to 68.8 years; PAF), 58.9 (52.3 to 65.4 years; MSA), and 19.2 (11.8 to 26.6 years; DBHD; $p = 0.005$ by Kruskal Wallis; $p = 0.275$ for MSA vs PAF by Mann-Whitney *U* test). Ages of patients with PAF and MSA were similar at the time of evaluation ($p = 0.176$). All 3 patient groups experienced profound orthostatic hypotension (table 1). Plasma levels of norepinephrine and its intraneuronal

Table 1 Orthostatic blood pressure and catecholamine data for patients[a]

Variable	PAF	MSA	DBHD	*p*	*p* (MSA vs PAF)
No.	12	10	4		
% Male	42	50	50	0.914	0.696
Disease duration, y	2.1 (0.2 to 3.9)	0.5 (−0.2 to 1.3)	NA	0.133	0.157
Supine systolic BP, mm Hg	145 (134 to 156)	147 (137 to 157)	103 (84 to 123)	0.010	0.757
Upright systolic BP, mm Hg	68 (57 to 79)	92 (75 to 110)	43 (10 to 76)	0.005	0.017
Orthostatic delta systolic BP, mm Hg	−77 (−91 to −63)	−55 (−70 to −39)	−53 (−53 to −53)	0.059	0.021
Supine norepinephrine, pg/mL	68 (43 to 93)	151 (88 to 213)	19 (−11 to 49)	0.001	0.003
Upright norepinephrine, pg/mL	111 (53 to 169)	260 (173 to 347)	28 (0 to 55)	0.001	0.006
Supine DHPG, pg/mL	650 (490 to 810)	1,050 (705 to 1,394)	14 (−7 to 36)	0.002	0.018
Upright DHPG, pg/mL	713 (558 to 869)	1,337 (797 to 1,877)	15 (−8 to 38)	0.001	0.010

Abbreviations: BP = blood pressure; DBHD = dopamine β-hydroxylase deficiency; DHPG = dihydroxyphenylglycol; MSA = multiple system atrophy; PAF = pure autonomic failure.
[a] Data are presented as mean (95% confidence interval).

Table 2 UPSIT test results[a]

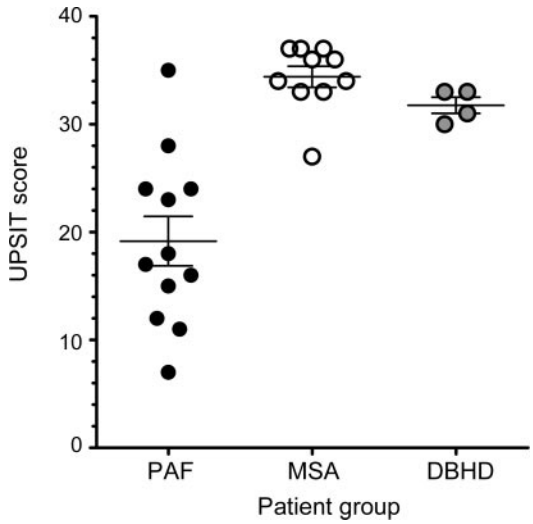
Variable	PAF	MSA	DBHD	p	p (MSA vs PAF)
Age at UPSIT, y	67.2 (61.5 to 72.9)	60.5 (54.1 to 66.9)	22.4 (11.2 to 33.6)	0.003	0.105
% Never smoked	73	70	75	0.980	0.890
UPSIT mean	19.2 (14.1 to 24.2)	34.4 (32.2 to 36.6)	31.7 (29.4 to 34.1)	<0.001	<0.001
Severe microsmia or anosmia, %	83	0	0	<0.001	<0.001

Abbreviations: DBHD = dopamine β-hydroxylase deficiency; MSA = multiple system atrophy; PAF = pure autonomic failure; UPSIT = University of Pennsylvania Smell Identification Test.
[a] Data are presented as mean (95% confidence interval).

metabolite, dihydroxyphenylglycol (DHPG), were highest in patients with MSA and consistent with diagnostic criteria.

Results of UPSIT. Results of UPSIT are shown in table 2. Patients with PAF had lower UPSIT scores (mean score of 19.2 [14.1 to 24.2]) than patients with MSA (34.4 [32.2 to 36.6]; $p < 0.001$) and patients with DBHD (31.7 [29.4 to 34.1]; $p = 0.015$) (figure 1). The differences between patients with PAF and those with MSA or DBHD persisted after adjustment for age ($p = 0.001$). Ten of 12 (83%) patients with PAF were severely microsmic or anosmic (figure 2); in contrast, olfactory function was normal in 70% of the patients with MSA. Three of the 4 patients with DBHD had mild microsmia and one had moderate microsmia.

Figure 1 University of Pennsylvania Smell Identification Test (UPSIT) scores



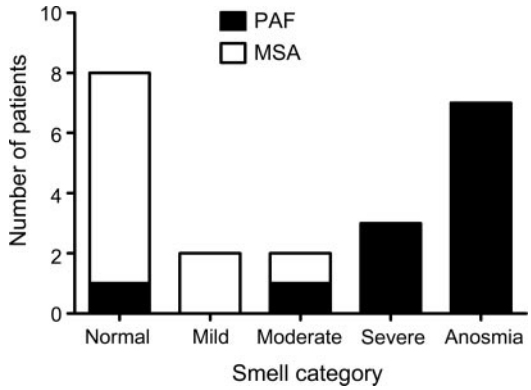
Individual scores (no. correctly identified of 40) from the UPSIT in patients with pure autonomic failure (PAF, black), multiple system atrophy (MSA, white), and dopamine β-hydroxylase deficiency (DBHD, gray). Horizontal bars indicate group mean values ± SEM. Mean score for PAF was significantly lower than for MSA ($p < 0.001$) and for DBHD ($p = 0.015$).

Approximately 75% of patients with MSA and patients with PAF were treated with fludrocortisone or midodrine. UPSIT scores were not different for treated (18.3 [11.4 to 25.2]) and untreated (21.7 [13.7 to 29.6]; $p = 0.354$) patients with PAF.

DISCUSSION The key findings of this study are as follows: 1) olfactory function was relatively unaffected in patients with DBHD, who have intact noradrenergic neurons but are unable to synthesize or release norepinephrine from those neurons; 2) odor identification was comparatively normal in MSA, despite loss of central neural pathways; and 3) olfactory function was clearly impaired in patients with PAF who have peripheral neuronal degeneration. These findings suggest that the UPSIT may therefore be useful in the differential diagnosis between MSA and PAF. The results from patients with DBHD suggest that the defect in PAF is not related to a peripheral deficiency of norepinephrine.

The etiology of olfactory dysfunction in neurodegenerative diseases has not been determined. The

Figure 2 Number of patients in olfactory categories



Number of patients with pure autonomic failure (PAF, black) and multiple system atrophy (MSA, white) in olfactory categories based on age- and gender-adjusted normative data. Note that 9 of 10 patients with MSA had normal olfactory function or mild microsmia, whereas 10 of 12 patients with PAF were anosmic or had severe microsmia.

odor identification pathway transmits signals from olfactory receptors in the nasal epithelium, to the mitral cells in the olfactory bulb, and via the olfactory tract to the amygdala and cortical areas.

Although the autonomic nervous system may affect the function of the olfactory receptors, by modulating the composition of the mucous secretion in the nasal passages,[18] the relatively normal UPSIT scores for MSA and DBHD are inconsistent with impaired olfactory receptor function secondary to autonomic impairment.

Abundant evidence supports a role for dopamine in odor detection[19,20] and odor discrimination,[21-23] although the specific dopamine receptors and their location in the olfactory pathway remain unclear. Olfactory dysfunction in PD has been attributed to dopaminergic denervation because deficits in both olfactory function and dopaminergic neurons can develop 2 to 7 years prior to the diagnosis of PD[24,25] and because inverse correlations are found between UPSIT scores and measures of dopaminergic deficiency in the striatum[2,5] and in the hippocampus, a structure involved in higher order processing of odor identification.[26] In contrast to this dopaminergic hypothesis for olfactory impairment in PD, olfactory function is normal in animal models of PD and in patients with MPTP-induced parkinsonism despite a dopaminergic deficit.[27] Olfactory function also does not seem to deteriorate as PD progresses and does not respond to dopaminergic medication.[4] Finally, patients with PD and patients with MSA may have similar degrees of dopaminergic denervation,[2] despite the superior olfactory function in MSA.[9]

The olfactory bulb and several cortical areas involved in olfactory processing are innervated by noradrenergic afferents.[28,29] Goldstein and Sewell[1] proposed that the documented loss of noradrenergic terminals in the heart in PAF and PD may also be reflected in the olfactory bulb and contribute to olfactory dysfunction.

Little information is available on norepinephrine levels in olfactory centers in PD, PAF, or other neurodegenerative diseases,[1] but they certainly cannot be lower than in DBHD, in which norepinephrine is undetectable due to the congenital absence of the DBH enzyme required for its synthesis. Patients with DBHD demonstrated preserved odor identification, which suggests that a norepinephrine deficit does not underlie impaired olfactory function in PD and PAF. It is also possible that patients with DBHD have developed some compensatory mechanism for modulating olfactory signals in the olfactory bulb. Interestingly, rats treated with an intrabulbar injection of 6-hydroxydopamine lack bulbar norepinephrine but retain dopamine and respond normally in odor detection tests.[30]

Neurons that degenerate in PD contain Lewy bodies, abnormal aggregates of α-synuclein, and other proteins. The deposition of Lewy bodies in PD in the olfactory bulb and the brainstem occurs early and then progresses to the midbrain, limbic system, and cortex.[31] PAF and MSA are also α-synucleinopathies involving neuronal Lewy bodies in PAF and glial inclusions in MSA. Neuronal degeneration in olfactory areas in PD and PAF could be related to synuclein deposition in those areas. The relatively normal olfactory function in patients with MSA suggests that hyposmia may relate to the specific pathology of Lewy bodies rather than to synuclein in general.[1]

Age, gender, and smoking experience did not appear to influence our findings. Olfactory function declines with aging, and is inferior in males,[18,32] but our patients with PAF and patients with MSA were similar in age and gender. Furthermore, group differences in odor identification remain even if UPSIT scores were normalized by age and gender. The proportion of individuals with a history of smoking was also similar in the 3 patient groups.

The effects of fludrocortisone and midodrine on olfactory function are unknown. Since they were used by a similar percentage of both PAF and MSA patient groups, and UPSIT scores were similar for patients with PAF, regardless of medication, the use of fludrocortisone and midodrine did not appear to influence UPSIT score.

Even though we cannot be certain that the differences in olfactory function reported here would be apparent in earlier stages of disease, our results suggest that UPSIT is useful in differentiating between PAF and MSA. In particular, the presence of severe microsmia or anosmia is indicative of PAF, and suggests that noradrenergic innervation is important for olfactory function. In contrast, olfactory function is preserved in patients with intact dopamine, but congenital absence of norepinephrine.

There are some limitations to our study. The number of patients studied was limited by the fact that these are rare disorders. Future larger studies are needed to confirm our findings and to assess the natural history of olfactory impairment in PAF.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Emily M. Garland.

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